REMARKS

Applicants thank the Examiner for entering the preliminary amendment filed on October 16, 2003. Claims 16, 18-25 and 27-33 are pending in this application and have been rejected. Applicants amend claims 16 and 25 to more clearly define claimed subject matter by introducing the phrase "promoted by an increase in IFN-γ and/or TNF-α levels." Support for this amendment can be found in the specification as-filed, for example, at least at page 3, lines 16-19; and page 6, lines 11-20. No new matter is added.

Written Description Rejection

The Examiner has rejected claims 21-24 and 30-33 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description support in the specification. In particular, the Examiner is contending that the specification does not set forth any written description for the limitations of "blocking formation of a heterodimer containing a 40 kD or a 35 kD subunit" and "allowing formation of a heterodimer containing a 40 kD or a 35 kD submit but blocking activity of the heterodimer." (10/05/04 Office Action at page 3).

Applicants disagree with the Examiner's understanding of the claimed invention. The claimed invention, is based at least in part, on the discovery that IL-12 induces an increase in levels of IFN-γ and/or TNF-α, which are involved in the promotion of many autoimmune conditions. The claimed invention solves this problem by providing antagonists of IL-12, use of which would be beneficial in treating an autoimmune condition promoted by an increase in the levels of IFN-γ and/or TNF-α.

The claims at issue are drawn to method of treating an autoimmune condition promoted by an increase in levels of IFN-γ and/or TNF-α using IL-12 antagonists, specifically IL-12 antibodies, which bind either the 40 kD subunit of IL-12 (claims 21-24) or the 35 kD subunit of IL-12 (claims 30-33), and where such antibodies either block formation of a heterodimer containing the 40 kD or the 35 kD subunit or allow formation of the heterodimer but block its activity.

I. Claim limitations are implicit in the disclosure of the specification as-filed

The limitations of "antibodies which block formation of a heterodimer containing the 40 kD or the 35 kD subunit" or "antibodies which allow the formation of the heterodimer but block its activity" are implicit in the disclosure of the instant specification as-filed.

The specification provides adequate written description support for the broad genus of IL-12 antagonists, including IL-12 antibodies which can bind the 40 kD and/or the 35 kD subunit of IL-12. For example, the specification discusses at page 6, line 21 that IL-12 antagonists include species that will bind IL-12 **or biologically active fragments thereof**. The specification further provides antibodies as an example of such antagonists, including monoclonal antibodies, polyclonal antibodies, chimeric antibodies and fragments thereof. *See*, specification at page 7, lines 1-5. The specification discusses that IL-12 is a heterodimeric protein comprised of 40 kD and 35 kD subunits. The specification further discusses that any form of IL-12 can be used in the methods of the invention. For example, IL-12 may be in the form of a heterodimer comprised of a 40 kD subunit disulfide-bonded to a 35 kD subunit or an individual

subunit of IL-12 may be used. *See*, specification at page 8, lines 5-20. Accordingly, it would be clear to one of ordinary skill in the art that antagonists that bind IL-12 or its fragments, may either bind IL-12 as a heterodimer, or they may bind a particular subunit of IL-12. Further, it is clear from the specification that those antagonists which block IL-12 function would be desirable as such antagonists would prevent an increase in IFN-γ and/or TNF-α levels. Since IL-12 typically exists as a heterodimer, it would be clear to one of ordinary skill that either blocking the formation of such a heterodimer or blocking its activity would block IL-12 function.

II. *In haec verba* support is not required for adequate written description

Applicants submit that courts have often noted that the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue. *See*, for example, *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1364, 67 U.S.P.Q.2d 1876, 1885 (Fed. Cir. 2003). Also, see *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779, 64 U.S.P.Q. 2d 1945, 1948-49 (Fed. Cir. 2002), where the Court stated:

> [T]he failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented.

Additionally, in *In re Wright*, 866 F. 2d 422, 425, 9 U.S.P.Q.2d 1649, 1652 (Fed. Cir. 1989), the Court reversed the Patent Office's rejection of a claim amendment which was not explicitly recited in the specification. The Court noted that while the limitation of "not permanently fixed" used in the claims was not used verbatim

in the specification, the specification did unequivocally teach the absence of permanently fixed microcapsules.

Applying this legal precedent to the instant case, Applicants submit that the specification as filed does not have to explicitly recite all limitations of the claimed invention. Applicants submit as discussed above, that one of ordinary skill in the art would be able to recognize based on the specification-as-filed, that the Applicants' invention encompasses antagonists both which either block the formation of a heterodimer containing the 40 kD or the 35 kD subunit or which allow the formation of such a heterodimer but block its activity, as these antagonists would be useful in blocking IL-12 function.

III. Patentee may claim methods of using antibodies to a fully characterized antigen

Further, in the art area of antibodies, the Federal Circuit has recognized that as long as an antigen is fully characterized, patentee may claim antibodies to such an antigen.

> [A]s long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen

See *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004). In fact, Applicants note that the written description guidelines issued by the U.S. Patent and Trademark office also discuss that as long as a specification provides characterization of an antigen, a patentee may claim antibodies that bind the antigen. For example, the U.S. Patent and Trademark Office provides an example in its guidelines which discusses that where the

specification teaches that an antigen has been isolated and is useful for a certain purpose and where the specification provides a protocol by which the antigen was isolated, the specification meets the requirements of adequate written description for the antibodies that bind the antigen even if the specification does not describe such antibodies. The U.S. Patent and Trademark Office recognizes that the general knowledge in the art is such that antibodies can be made against virtually any protein. *See* pages 59 and 60 of the written description guidelines (http://www.uspto.gov/web/menu/written.pdf).

Applying this legal precedent to the instant case, Applicants submit that the instant specification fully describes the IL-12 protein, including how to purify the IL-12 heterodimer and its subunits. For example, the specification discusses at page 8, line 21 to page 9, line 22, that IL-12 or any subunit or fragment of IL-12, including the 35 kD and the 40 kD subunits may be produced recombinantly. The specification at page 10, lines 1-14, also provides suitable expression vectors and host cells that may be used for expressing IL-12 or subunits thereof. Further, the specification discusses biochemical purification techniques that can be used for purifying IL-12 or a subunit thereof. *See* specification at page 10, line 15 to page 12, line 13. Accordingly, based on the specification, one of ordinary skill in the art can easily purify IL-12 including the individual subunits and can easily make an antibody that binds IL-12 or binds a subunit thereof.

In view of the foregoing, Applicants respectfully submit that the instant specification provides adequate written description for all antibodies which bind one or

both subunits of IL-12, including antibodies which either block the formation of a heterodimer containing the 40 or the 35 kD subunit, or which allow the formation of such a heterodimer but block its activity.

Enablement Rejection

Claims 16, 18-25 and 27-33 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. In particular, the Examiner alleges that the specification has not taught that an antagonist or an antibody that binds to the 40 kD or a 35 kD subunit of IL-12 can be used to treat any autoimmune condition. (10/05/04 Office Action at page 4). In particular, the Examiner contends that the state of the art has not shown definitively that IL-12 antagonists or antagonists that bind the 40 kD or 35 kD subunit can be used to treat or prevent the numerous autoimmune conditions or diseases. (10/05/04 Office Action at pages 5 and 6). The Examiner appears to rely on certain references as allegedly discussing the unpredictability of the state of the art. Additionally, the Examiner alleges that the specification has not taught that an antagonist which binds the 40 kD or the 35 kD subunit of IL-12 can be used to treat any autoimmune condition (10/05/04 Office Action at page 4).

Applicants respectfully traverse this rejection. Applicants disagree with the Examiner's understanding of the references cited. Applicants discuss enablement for antagonists which bind each of the IL-12 subunits separately.

I. Antagonists which bind the 40 kD subunit of IL-12

Claims 16 and 18-24 are directed to use of antagonists which bind the 40 kD subunit of IL-12 for treating autoimmune diseases. First, Applicants submit that the claims at issue are not directed to any autoimmune disease as alleged by the Examiner, but to those autoimmune diseases which are promoted by an increase in IFN-γ and/or TNF-α levels. Second, Applicants note that the references cited by the Examiner herself provide enabling disclosure for the antagonists which bind the 40 kD subunit to treat various autoimmune diseases. For example, among the references cited by the Examiner, Kim et al. (The Role of IL-12 in Inflammatory Activity of Patients with Rheumatoid Arthritis (RA), Clin. Exp. Immunol. 119: 175-181 (2000)) ("*Kim*"); Fox et al. (Anti-Interleukin-12 Antibody, BioDrugs 13(4): 233-241 (2000)) ("*Fox*"); and Luciano Adorini (Immunotherapeutic Approaches in Multiple Sclerosis, J. Neurol. Sci. 223: 13-24 (2004)) ("*Adorini*") all appear to suggest that antagonists of IL-12 can be used for treatment of autoimmune diseases. *Kim* discusses blocking IL-12 as being beneficial for treatment of rheumatoid arthritis. *See* Abstract. Similarly, *Fox* discusses that antibodies that block IL-12 can prevent relapses of experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis. *See* Abstract. Additionally, *Adorini* discusses at page 17, column 2, that anti-IL-12 monoclonal antibody treatment prevents superantigen-induced EAE, an animal model for multiple sclerosis, and subsequent relapses. It further discusses that IL-12 antagonists can be useful in the treatment of other autoimmune conditions, such as inflammatory bowel disease. *Id.* While these references do not explicitly discuss whether the antagonists that were used

bind the 35 kD or the 40 kD subunit of IL-12, they cite to other references which discuss that these antagonists bind the 40 kD subunit of IL-12. *See*, for example, Wysocka et al. (Eur. J. Immunol. 25:672-676 (1995)) which describes antibodies to the 40 kD subunit of IL-12 that were referenced in *Adorini*. Similarly, *Fox* cites to another reference which also discusses antibodies to the 40 kD subunit of IL-12. *See*, for example, Neurath et al. (J. Exp. Med. 182: 1281-90 (1995)). Applicants enclose a courtesy copy of these references for the Examiner's convenience.

Accordingly, each of these references only provide further enabling disclosure for using an antibody that binds the 40 kD subunit of IL-12 in treating various autoimmune diseases.

The Examiner appears to be concerned about Bensen et al. (The Role of IL-23 in Experimental Autoimmune Encephalomyelitis, FASEB J. 16(5): A1045 (2002)) ("*Bensen*") as allegedly indicating that IL-23 and not IL-12 may have a dominant role in chronic autoimmune disease. (10/05/04 Office Action at page 4). Applicants submit that this observation is irrelevant to the claims drawn to the use of antagonists which bind the 40 kD subunit of IL-12. The fact that some of these antagonists may also bind IL-23, is irrelevant to the instant claims as the claims do not exclude the antagonists from binding other cytokines.

In view of the foregoing, Applicants submit that the state of the art is not unpredictable with respect to antagonists that bind the 40 kD subunit of IL-12 as each of the references cited have shown that antagonists that bind the 40 kD subunit of IL-12

are useful for treating autoimmune conditions. Accordingly, Applicants request that this rejection be reconsidered and withdrawn.

II. Antagonists which bind the 35 kD subunit of IL-12

Claims 25 and 27-33 are drawn to the use of antagonists which bind the 35 kD subunit of IL-12 to treat autoimmune diseases.

Applicants submit that even if a nonfunctional variant exists, it does not necessarily render a claim nonenabled. *Atlas Powder Co. v. E.I. duPont de Nemous & Co.*, 750 F.2d 1569, 1577, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984); MPEP § 2164.08 (b). The specification provides screening assays and animal models, that can be used for testing antibodies that bind IL-12 for their ability to treat autoimmune conditions promoted by an increase in IFN-γ and/or TNF-α levels.

Nonstatutory Double Patenting Rejection

Claims 16, 18-22 and 27-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting rejection as being unpatentable over claims 16 and 22 of co-pending U.S. Patent Application No. 09/512,701.

Applicants respectfully traverse this rejection, but, at this time, ask that this rejection be held in abeyance until allowable subject matter is determined. At that time, Applicants will consider whether to file a Terminal Disclaimer.

CONCLUSION

In view of the foregoing, Applicants respectfully request the entry of this Amendment, the Examiner's reconsideration and the timely allowance of all the claims. Should the Examiner feel that this application is not in condition for allowance, Applicants request that the Examiner contact the undersigned representative at 202-408-4086.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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